Interstitial Cystitis—Epidemiology, Diagnostic Criteria, Clinical Markers

Philip M. Hanno, MD

Division of Urology, Hospital of the University of Pennsylvania, Philadelphia, PA

Knowledge of the epidemiology of interstitial cystitis (IC), the burden of the disease in the population, and the identification of possible risk factors remains largely fragmentary. The most reliable information comes from the few population-based studies that have appeared in the literature over the past 25 years, but two major issues urgently need to be addressed by appropriate epidemiologic studies: although studies find that only 10% of IC occurs in men, the hallmark symptoms of chronic prostatitis—pelvic pain, voiding dysfunction, and pain associated with sexual activity—overlap with those in men who carry the IC diagnosis. In addition, it is not known whether children suffer from the condition. The definition of IC is grounded in the symptomatology of pelvic pain and urinary frequency of a chronic nature and unexplained by any known urologic or other system pathology, but undue reliance on cystoscopic criteria has undoubtedly led to significant underdiagnosis. Efforts to identify clinical markers for diagnosis of IC are continuing and may lead the way to ascertaining the etiology and pathophysiology of IC. [Rev Urol. *2002;4(suppl 1):S3–S8*]

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Knowledge of the epidemiology of interstitial cystitis (IC), the burden of the disease in the population, and the identification of possible risk factors remains largely fragmentary.[1] Much of our knowledge has historically come from anecdotal reports or large series of cases from individual institutions. Perhaps the most reliable information can be gleaned from the few population-based studies that have appeared in the literature over the past 25 years.

The first population-based study[2] included "almost all the patients with interstitial cystitis in the city of Helsinki." In a population of 1,000,000 persons, the

prevalence of IC in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. The annual incidence of new female cases was 1.2 per 100,000. Severe cases accounted for 10% of the total, and 10% of cases were in men. The disease onset was noted to be generally subacute rather than insidious, with the full development of the classic symptom complex taking place over a relatively short time. Oravisto[2] noted that the disease reaches its final state rapidly, and that subsequent major deterioration in symptom severity was the exception rather than the rule.

Much of our knowledge has historically come from anecdotal reports.

Fifteen years later, a population-based study[3] in the United States confirmed many of the conclusions reached by Oravisto. Among the findings were the following:

1. In 1987 there were 43,500 (perhaps up to 90,000) diagnosed cases of IC in the United States, approximately twice the prevalence in Finland. Women who were diagnosed as actually having IC represented only 20% of the cases presenting with symptoms (chronic painful bladder, sterile urine) that were suggestive of this diagnosis. Thus one could extrapolate a prevalence of the disorder of up to 500,000 persons, depending upon the assumptions used.
2. Median age of onset is 40 years.
3. Late deterioration in symptoms is unusual.
4. Up to 50% of patients experience spontaneous remission with a duration ranging from 1 to 80 months (mean 8 months).
5. Patients with IC are 10 to 12 times more likely than controls to report childhood bladder problems.
6. Patients with IC are twice as likely as controls to report a history of urinary tract infection.
7. Household size, marital status, number of male sexual partners, and educational status did not differ from a control population.
8. Persons of Jewish origin made up 14% of the IC population but only 3% of the control population, a finding later substantiated by Koziol.[4]
9. Quality of life of IC patients was lower than that of patients undergoing chronic dialysis for renal failure. (Others have positioned IC quality of life as below that of hypertension but better than rheumatoid arthritis.[5])

The Held study,[3] however, may actually underestimate the footprint of the disease. Jones and Nyberg published a study relying on self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey of 20,561 adults.[6] They calculated that 1,000,000 people in the United States would report having a diagnosis of IC in 1990, more than double the maximum figure in the Held study. Using the Nurses' Health Study I and II as the basis of information, Curhan and colleagues concluded that the prevalence of interstitial cystitis was between 52 and 67 per 100,000, figures at least 50% greater than reported by Held.[7]

Major deterioration in symptom severity was the exception rather than the rule.

Allergies, fibromyalgia, and inflammatory bowel disease are overrepresented in the IC population.[8] Whether there exists a genetic susceptibility to IC is as yet unknown, but studies on twins suggest there may be.[9]

Two major issues, among many others, urgently need to be addressed by appropriate epidemiologic studies. 1) Although studies find that only 10% of IC occurs in men, the potential figure is much larger. The hallmark symptoms of chronic prostatitis—pelvic pain, voiding dysfunction, and pain associated with sexual activity—overlap with those in men who carry the IC diagnosis.[1] Comparative studies examining chronic prostatitis (chronic pelvic pain syndrome in men) and interstitial cystitis are necessary to determine if these two conditions are actually one and the same. 2) It is not known whether children suffer from interstitial cystitis. Apart from the few anecdotal experiences reported in the literature, this is largely virgin territory. With the advent of noninvasive markers in the future to help establish the IC diagnosis, and with the help of longitudinal follow-up studies of children over months and years, we may learn if urinary frequency and urgency in childhood represent a form of this disorder.

National Institute of Diabetes and Digestive and Kidney Diseases Criteria

There is some truth to the notion that interstitial cystitis remains a "great enigma" and that in some respects our understanding of the disease and that of Hunner 100 years ago are not markedly different.[10] A definition of IC has been hampered by the lack of

specific diagnostic criteria, the lack of specific histopathologic changes, the unpredictable fluctuation in symptoms, and the extreme variability among patients in terms of symptoms, objective findings, and treatment responses. The diagnosis is almost an "Aunt Minnie"—that is, I can't define it but I know it when I see it. It is grounded in the symptomatology of pelvic pain and urinary frequency that is of a chronic nature and unexplained by any known urologic or other system pathology.

The National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) held workshops in August 1987 and November 1988 at which consensus criteria were established for the diagnosis of IC.[11] These criteria were not meant to define the disease, but to ensure that groups of patients studied would be relatively comparable. They are listed in Table 1.

In the void of the IC universe, these criteria seemed to become almost a *de facto* definition of IC, and what had been intended as a tool for research studies may have unwittingly left many patients' symptoms undiagnosed and possibly untreated if they did not meet the strict standards laid out.

Fortunately, the NIDDK had developed a multi-institutional database study that later served to resolve this issue. The Interstitial Cystitis Data Base Study (ICDB) was a large, observational study designed to determine the treated history of IC patients and identify common patient characteristics.[12] Entry requirements for the ICDB were considerably less stringent than the NIDDK criteria, commensurate with their different perceived role: to include *all* IC-like patients, with the intention of being able to follow the progression of the disease, as well as to include all subgroups that might help identify the nature and the extent of the syndrome.

Table 1
The National Institute of Diabetes and Digestive and Kidney Diseases Consensus Criteria for the Diagnosis of Interstitial Cystitis

To be diagnosed with interstitial cystitis, patients must have either:	
Glomerulations on cystoscopic examination	Or a classic Hunner's ulcer
and either:	
Pain associated with the bladder	Or urinary urgency
An examination for glomerulations should be undertaken after distention of the bladder under anesthesia to 80–100 cm of water pressure for 1–2 minutes. The bladder may be distended up to two times before evaluation.	
The glomerulations must:	
Be diffuse—present in at least 3 quadrants of the bladder	
Be present at a rate of at least 10 glomerulations per quadrant	
Not be along the path of the cystoscope (to eliminate artifact from contact instrumentation).	
The presence of any one of the following criteria excludes the diagnosis of interstitial cystitis:	
1. Bladder capacity of greater than 350 cc on awake cystometry using either a gas or liquid filling medium	
2. Absence of an intense urge to void with the bladder filled to 100 cc of gas or 150 cc of water during cystometry, using a fill rate of 30–100 cc/min	
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described above	
4. Duration of symptoms less than 9 months	
5. Absence of nocturia	
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics	
7. A frequency of urination, while awake, of less than 8 times per day	
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period	
9. Bladder or ureteral calculi	
10. Active genital herpes	
11. Uterine, cervical, vaginal, or urethral cancer	
12. Urethral diverticulum	
13. Cyclophosphamide or any type of chemical cystitis	
14. Tuberculous cystitis	
15. Radiation cystitis	
16. Benign or malignant bladder tumors	
17. Vaginitis	
18. Age less than 18 years	

Table 2
The Interstitial Cystitis Data Base Study Entry Requirements

1. Providing informed consent to participate in the study
2. Willing to undergo a cystoscopy under general or regional anesthesia, when indicated, during the course of the study
3. At least 18 years of age
4. Having symptoms of urinary urgency, frequency, or pain for more than 6 months
5. Urinating at least 7 times per day, or having some urgency or pain (measured on linear analog scales)
6. No history of or current genito-urinary tuberculosis
7. No history of urethral cancer
8. No history of or current bladder malignancy, high-grade dysplasia, or carcinoma in situ
9. Males: no history of or current prostate cancer
10. Females: no occurrence of ovarian, vaginal, or cervical cancer in the previous 3 years
11. Females: no current vaginitis, clue cell, trichomonas, or yeast infections
12. No bacterial cystitis in previous 3 months
13. No active herpes in previous 3 months
14. No antimicrobials for urinary tract infections in previous 3 months
15. Never having been treated with cyclophosphamide (Cytoxan)
16. No radiation cystitis
17. No neurogenic bladder dysfunction (eg, due to a spinal cord injury, a stroke, Parkinson's disease, multiple sclerosis, spina bifida, or diabetic cystopathy)
18. No bladder outlet obstruction (determined by urodynamic investigation)
19. Males: no bacterial prostatitis for previous 6 months
20. Absence of bladder, ureteral, or urethral calculi for previous 3 months
21. No urethritis for previous 3 months
22. Not having had a urethral dilation, cystometrogram, bladder cystoscopy under full anesthesia, or a bladder biopsy in previous 3 months
23. Never having had an augmentation cystoplasty, cystectomy, cystolysis, or neurectomy
24. Not having a urethral stricture of less than 12 French

Entry requirements are outlined in Table 2.

The most striking difference between the ICDB study eligibility criteria and the NIDDK criteria was that baseline cystoscopy was not mandatory. The specificity of glomerulations—submucosal hemorrhages visible after distention of an IC bladder—has been questioned,[13] as has the sensitivity of this finding,[14] often considered the *sine qua non* of an IC diagnosis. Undue reliance on the cystoscopic criteria for the diagnosis of IC has undoubtedly led to significant underdiagnosis of IC. On the other hand, up to 70% of men with symptoms of nonbacterial prostatitis and prostatodynia have glomerulations and submucosal hemorrhages when undergoing bladder distention under anesthesia, raising the possibility that some cases of prostatitis may actually be interstitial cystitis.[15]

A critical evaluation of the ICDB criteria and the NIDDK criteria has shown that the NIDDK criteria are far too restrictive to be useful either to clinically define IC or to provide a workable set of diagnostic criteria. Only 32% of patients evaluated fully by NIDDK standards would have been diagnosed with IC by those criteria. Even of patients partially studied, only 42% would have been in compliance. Conversely, the criteria did uphold their intended purpose, as there was almost universal agreement among the specialists that patients meeting the criteria did exhibit the clinical syndrome of IC.[16]

Clinical Markers

The idea of a clinical marker to diagnose interstitial cystitis is complicated by the fact that IC, as we currently understand it, is essentially a *symptom complex* diagnosed by excluding known causes of the symptoms. It is unlikely that any marker will have 100% specificity and 100% sensitivity, and if it did, we would not need it, because the symptoms would then be just as accurate as the marker. Therefore, to be useful, a marker must tell us something more than we already know. If it could help us determine disease progression or prognosis, then it would aid our patient management in those who were marker-positive. If it could help predict response to specific therapies, then in marker-positive patients we could more rationally dispense treat-

Table 3
Change in Clinical Interstitial Cystitis Markers After Treatment

Marker	Treatment	Change
Nitric oxide synthase Cyclic guanosine monophosphate	Oral L-arginine	Increased
Eosinophilic cationic protein	Subcutaneous heparin	Decreased
Prostaglandin E2 Kallikrein	Bladder distention	Decreased
Neutrophil chemotactic activity	Intravesical dimethyl sulfoxide (DMSO)	Decreased
Interleukins: IL-2, IL-6, IL-8	Intravesical BCG	Decreased
IL-2	Oral nifedipine	Decreased
Antiproliferative factor Heparin-binding epidermal growth factor	Sacral nerve stimulation	Decreased

Data from Erickson D. Urine markers of interstitial cystitis. *Urology*. 2001;57:15–21.

ment. If it could separate out IC from competing causes of similar symptoms in patients in whom we cannot exclude pathologies such as endometriosis, prostatitis, or chronic low-grade infection as a primary problem, it might limit unnecessary and sometimes unproductive diagnostic testing. As yet we do not have such a marker, but much effort is going into finding one.

The idea that the urine of IC patients is itself carrying a pathologic substance accounting for the disorder is attractive. Most current theories of pathogenesis involve access of a component of urine to the interstices of the bladder wall, resulting in an inflammatory response induced by toxic, allergic, or immunologic means. The substance in the urine may be a naturally occurring one—a substance that acts as an initiator only in particularly susceptible individuals—or may act like a true toxin, gaining access to the urine by a variety of mechanisms or metabolic pathways.[17]

Keay and her group at the University of Maryland have reported compelling data regarding an antiproliferative factor (APF) in IC urine that inhibits primary bladder epithelial cell proliferation. She has shown significantly decreased levels of heparin-binding epidermal growth factor-like growth factor (HB-EGF) and increased levels of epidermal growth factor (EGF) compared with urine from asymptomatic controls and patients with bacterial cystitis. This information is nicely reviewed in a recent paper in which she sought to confirm the specificity of these findings for IC using a larger patient population of normal controls as well as patients with a variety of non-IC urogenital disorders.[18] APF activity was present significantly more often in IC than in control urine specimens, with a 94% specificity and 95% sensitivity for IC versus all controls. Similar findings were found as predicted for HB-EGF and EGF.

GP-51 is a glycoprotein in the transitional epithelium of humans, rabbits, and other mammals. It can be isolated from human urine. Byrne and colleagues noted decreased staining for GP-51 in IC bladder biopsies compared to controls.[19] Mean urine levels in IC patients were also lower than controls. The significance of these findings remains to be determined.

Erickson has contributed much to our knowledge of putative markers for IC. Her recent meta-analysis of the literature noted many instances of markers that changed after various treatments[20] (see Table 3).

The study of markers is an exciting area, now at the forefront of IC

Main Points

- Comparative epidemiologic studies examining chronic prostatitis (chronic pelvic pain syndrome in men) and interstitial cystitis (IC) are needed to help determine if these two conditions are actually one and the same.
- IC is a clinical syndrome and a diagnosis of exclusion. The National Institute of Diabetes & Digestive & Kidney Diseases criteria should not be relied upon to make the diagnosis in clinical practice.
- Patients with a symptom constellation of chronic frequency, pelvic pain or pressure, and sensory urgency can be considered to have IC when all other causes of these symptoms have been reasonably ruled out.
- The possibility now exists that in the foreseeable future a urinary marker of IC may become available. Marker(s) may help with diagnosis, treatment, and follow-up of IC patients.

research. It may lead the way to ascertaining the etiology and pathophysiology of interstitial cystitis. It is hoped that a marker or markers will be found that can make definitive diagnosis in the face of competing possible symptom etiologies, allow a rational treatment algorithm, reassure the patient as to prognosis, and become an adjunctive measure in following the clinical course of the disease. ■

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